Clinical review

Science, medicine, and the future

New pacing technologies for heart failure

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Heart failure is a sizeable problem in elderly populations, and although pharmacological treatment has improved, outcome generally remains poor. New pacing technologies have been developed to treat heart failure, with promising results

The prevalence of heart failure in the general population is estimated to be 1-2% and increases rapidly with age.[1] In developed countries heart failure is a leading cause of admission to hospital among elderly patients and accounts for 1-2% of healthcare expenditure.[2] Although several pharmacological treatments have improved outcome,[3–5] the prognosis of patients with heart failure remains poor. Alternative non-pharmacological approaches including cardiac transplantation have been limited by availability of organs, and the use of artificial left ventricular assist devices remains restricted.

Recently, several promising new developments have taken place in pacing technology to treat selected patients with heart failure. These include atrio-biventricular pacing to correct abnormal patterns of left ventricular contraction and implantable cardiac defibrillators for treatment of malignant ventricular arrhythmias. As the scale of the problem becomes apparent new treatments that have been shown to improve morbidity and possibly mortality in patients with chronic heart failure will undoubtedly have a major impact on clinical practice and healthcare resources.

Summary box

New pacing technologies may now be used to treat selected patients with heart failure

Atrio-biventricular pacing has been shown to improve symptoms and reduce admission to hospital in patients with left bundle branch block and heart failure

The results of randomised trials powered to test mortality benefits from biventricular pacing will soon be available

Implantable defibrillators reduce mortality in survivors of sudden cardiac death and patients with ventricular arrhythcardiac and poor left ventricular function; recent clinical trials show that indications for the use of these devices will be expanding

The use of combined implantable defibrillators and atrio-biventricular pacemakers for patients with heart failure is likely to increase—clear indications for such devices are beginning to emerge

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Methods

Sources and search criteria

We systematically searched PubMed for publications on chronic heart failure and biventricular pacing, cardiac resynchronisation, and implantable cardioverter defibrillators for the years 1985-2003.

The heart failure population

In the developed world the underlying cardiac abnormality for most patients with heart failure is impaired left ventricular systolic function due to ischaemic heart disease or idiopathic dilated cardiomyopathy.[6] Despite maximal drug treatment many patients still experience symptoms on minimal exertion or even at rest (New York Heart Association class III-IV), and this functional limitation often has a marked impact on their quality of life. Recurrent and prolonged hospital admissions for periods of decompensation of the heart failure syndrome are common in these patients.[7] The prognosis for people with heart failure remains poor. In clinical trials, death is most commonly due to either malignant ventricular tachyarrhythmias or progressive pump failure. Population based studies report a mortality of close to 40% within one year of diagnosis and around 10% per year thereafter.[7] For patients who remain symptomatic at rest despite maximal medical treatment annual mortality may be as high as 40%.[8]

Ventricular dyssynchrony

An estimated 30% of patients with chronic heart failure have evidence of abnormal interventricular conduction on the 12 lead electrocardiogram, most often in the form of left bundle branch block. The resultant abnormal activation of the myocardium

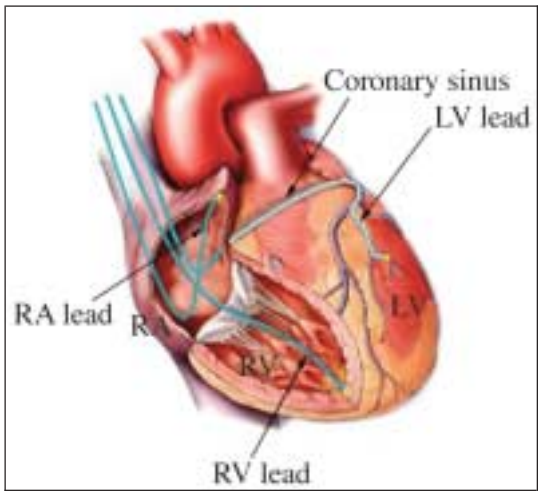

Fig 1 The anterior walls of the right atrium and ventricle have been removed to show the lead arrangements used in biventricular pacing. Tributaries that drain the left ventricle form the coronary sinus, which opens posteriorly into the right atrium. The left ventricular lead shown is positioned in the antero-lateral cardiac vein, with conventional pacing leads in the right atrial appendage and right ventricular apex (RA=right atrium; RV=right ventricle; LV=left ventricle). Used with permission from the authors (AWCC)

causes deranged ventricular contraction or dyssynchrony, with regions of early and late contraction. Typically, the interventricular septum contracts early relative to the delayed contraction of the lateral free wall of the left ventricle. In its most severe form dyssynchrony can result in contraction of the septum while the lateral wall is relaxing and vice versa. If opposing ventricular walls fail to contract together, a sizeable proportion of blood is simply shifted in the ventricular cavity instead of being ejected into the circulation, thereby reducing cardiac output. The proportion of the cardiac cycle available for left ventricular filling and ejection is reduced by dyssynchronous contraction, which further contributes to a decrease in the pumping ability of the heart. Even in structurally normal hearts the presence of left bundle branch block impairs cardiac ejection fraction. In patients with chronic heart failure and poor systolic function ventricular dyssynchrony further compromises cardiac performance and may exacerbate symptoms of heart failure.

Pacing for the treatment of heart failure

Permanent pacing has been used for many years to treat symptomatic bradycardia and may alleviate heart failure when associated with heart block. Several studies have examined the use of conventional dual chamber atrio-right ventricular pacing for the treatment of heart failure, in the absence of symptomatic bradycardia or heart block, in an attempt to enhance cardiac performance, but results have been inconsistent.[9 10] In most studies, right ventricular pacing produced no haemodynamic benefit or had detrimental effects on left ventricular function. This probably reflects the fact that right ventricular apical pacing (which creates a left bundle branch block pattern) induces ventricular dyssynchrony, with detrimental effects on overall pump function of the heart. Many centres now advocate pacing from the right ventricular septum to provide a more physiological pattern of ventricular activation. With a greater understanding of the consequences of deranged ventricular conduction came the proposal of using more sophisticated pacing configurations in an attempt to correct or normalise electrical activation and improve cardiac performance. This has evolved to form the basis of the concepts for cardiac resynchronisation.

Cardiac resynchronisation

Cardiac resynchronisation or biventricular pacing entails inserting pacing leads via the cephalic or subclavian veins into the right atrium and right ventricle, as in conventional dual chamber permanent pacing. In addition, however, a third pacing lead is used to pace the left ventricle. In early studies this was achieved by performing a thoracoscopic procedure with placement of the electrode on the epicardial left ventricular free wall.[11 12] This necessitated general anaesthesia and therefore carried appreciable risk in a high risk group of patients. In 1998 Daubert et al published the results of a study of a fully transvenous permanent biventricular pacing system,[13] which revolutionised the technique (fig 1). Specially designed catheters are inserted through the subclavian vein and passed down into the right atrium, from where the left ventricular coronary venous circulation can be accessed. The coronary venous system consists of a series of tributaries overlying the ventricular myocardium. They drain into the coronary sinus that opens into the right atrium. This network of coronary venous branches can be visualised by performing a coronary sinus venogram (fig 2) and used to guide the placement of the left ventricular pacing lead. The three pacing electrodes are then connected to the artificial pacemaker to allow biventricular pacing (fig 3).

Effects of biventricular pacing

Biventricular pacing aims to restore synchronous cardiac contraction. Studies have shown that when ventricular dyssynchrony is reduced the heart is able to contract more efficiently and increase left ventricular

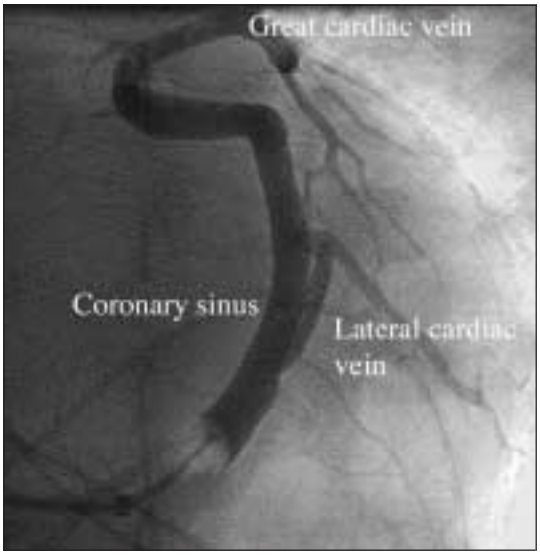

Fig 2 Coronary sinus venogram taken with a veno-occlusive balloon (V) inflated. Left ventricular tributaries from the great cardiac vein and a lateral cardiac vein are shown draining into the coronary sinus. Used with permission from the authors (AWCC)

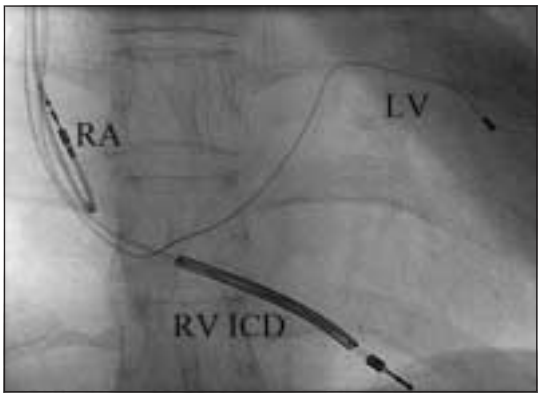

Fig 3 Fluoroscopy showing final lead positions of an atrio-biventricular implantable cardiac defibrillator in an antero-posterior projection (RA=right atrial lead; RV ICD=right ventricular implantable defibrillator lead; LV=left ventricular coronary sinus lead). Used with permission from the authors (AWCC)

ejection fraction and cardiac output while working less and consuming less oxygen.[14] In addition, reintroducing left ventricular synchrony can increase left ventricular filling times, decrease pressure on the pulmonary capillary wedge, and reduce mitral regurgitation (box 1). More advanced devices now enable manipulation of both atrioventricular and interventricular pacing intervals and the potential to further optimise individual haemodynamic and functional improvement.

Clinical trials of biventricular pacing

Clinical trials have shown that biventricular pacing is effective in the treatment of heart failure patients with left bundle branch block (table). Several randomised controlled clinical trials have compared biventricular pacing with medical treatment on its own. Both the multisite stimulation in cardiomyopathies (MUSTIC) and the multicentre insync randomised clinical evaluation (MIRACLE) studies, which enrolled 68 and 524 heart failure patients, respectively, in a randomised crossover trial of biventricular pacing showed significant improvements in quality of life scores, exercise tolerance, New York Heart Association functional class, peak oxygen uptake, and cardiac ejection fraction during biventricular pacing.[15 16] What was particularly impressive was the reduction in admissions to hospital for worsening heart failure seen in the MIRACLE study. At six months the relative risk of decompensated heart failure requiring admission to hospital was reduced by 50% in the group receiving biventricular pacing, and a staggering 77% reduction of total hospital days saved for treating heart failure was observed in the paced group compared with the control group. As the clinical trial lasted only six months it is still uncertain whether the benefits of biventricular pacing will be sustained or increased with a longer period of follow up. Thus the benefits seen with biventricular pacing not only seem to improve the quality of life for individual patients but also indicate that important and substantial economic savings may arise from using this technology.

As yet no definitive published data are available on the effects of biventricular pacing on mortality, but several studies with end points of cardiac and all cause mortality remain in progress.[17 18] The cardiac resynchronisation in heart failure (CARE-HF) study has recently completed recruitment of patients, whereas the preliminary findings of the comparison of medical treatment, pacing, and defibrillation in chronic heart failure (COMPANION) study, which randomised over 1600 patients to medical treatment alone, to biventricular pacing, and to biventricular implantable cardiac defibrillators have been announced. This study was halted prematurely because of a 20% reduction in all cause mortality and all cause admissions to hospital in the groups receiving biventricular pacing. The most notable benefits were seen in the arm of the study in which patients received biventricular implantable cardiac defibrillators, where a 40% reduction of all cause mortality was achieved. Publication of the full report is eagerly awaited, but these preliminary data indicate that biventricular pacing may confer important mortality benefits.

Box 1: Haemodynamic effects of biventricular pacing

- Increased left ventricular ejection fraction and fractional shortening
- Increased cardiac output
- Prolonged diastole and left ventricular filling time
- Reduced left ventricular end diastolic and end systolic volumes
- Increased left ventricular synchrony and pulse pressure
- Increased peak oxygen uptake
- Decreased pulmonary capillary wedge pressure
- Decreased mitral regurgitation

Box 2: Who should be considered for biventricular pacing

- Systolic heart failure
- Non-reversible cause
- Highly symptomatic (New York Heart Association class III-IV)
- Optimal medical therapy
- Ventricular dyssynchrony:
  Left bundle branch block wide QRS > 130 ms/echo assessment
  Induced by right ventricular apical pacing
- Sinus rhythm
- Significant mitral regurgitation

Limitations and complications of biventricular pacing

The electrocardiogram is used as the screening tool for predicting ventricular dyssynchrony and hence suitability for biventricular pacing. Up to 20% of patients fulfil the criteria for biventricular pacing (box 2), yet derive little or no clinical benefit from resynchronisation.[19] In the future, more sensitive and specific non-invasive screening tests will be required to improve the selection of patients. This will probably be in the form of echocardiography guided techniques such as tissue Doppler echocardiography, which facilitates the quantification of dyssynchrony[20] and thus may provide more accurate prediction of a favourable clinical response with biventricular pacing.

Clinical trials of atrio-biventricular pacing

Trial	Design	No of patients randomised	Inclusion criteria	End points	Outcome
Path CHF (left ventricular lead placed epicardially with thoractomy)	Single blind randomised control crossover trial of cardiac resynchronisation treatment, placebo or univentricular pacing	41	New York Heart Association score III/IV Quality of life score >120 ms PR >150 ms	New York Heart Association score Quality of life score Distance covered by 6 minute walk Peak oxygen uptake	Decreased* Decreased* Increased* Increased* (Similar benefits seen with CRT and univentricular (LV) stimulation)
InSync	Prospective observational study	117	New York Heart Association score III/IV QRS >150 ms Left ventricular ejection fraction <35%	New York Heart Association score Quality of life score Distance covered by 6 minute walk	Decreased* Improved* Increased*
MUSTIC	Single blind randomised control crossover trial of cardiac resynchronisation treatment or placebo	48 3 months each arm	New York Heart Association score III QRS >150 ms Ejection fraction <35%	Distance covered by 6 minute walk Quality of life score Peak oxygen uptake Admission to hospital	Increased* Improved* Increased* Decreased*
MIRACLE	Double blind randomised controlled trial	453 (228 to cardiac resynchronisation) 6 month follow up	New York Heart Association score III/IV QRS >130ms Ejection fraction <35%	Distance covered by 6 minute walk New York Heart Association class Quality of life score Ejection fraction Hospitalisation	Increased* Decreased* Improved* Increased* Decreased*
COMPANION	Randomised controlled trial of cardiac resynchronisation treatment, cardiac resynchronisation therapy and implantable cardiac defibrillator, or placebo	>1600	New York Heart Association score III/IV QRS >120 ms Ejection fraction <35%	All cause mortality Cardiovascular hospitalisations	Decreased with cardiac resynchronisation and cardiac resynchronisation+implantable cardiac defibrillators* Trial terminated prematurely owing to survival benefits with cardiac resynchronisation and ICD arms. Full results expected 2003
CARE-HF	Randomised controlled trial of cardiac resynchronisation treatment or placebo	800 (400 to cardiac resynchronisation) 18 month follow up	New York Heart Association score III/IV QRS >150 ms or >120 ms with dyssynchrony on echo Ejection fraction <35%	All cause mortality Cardiovascular admissions to hospital Echo parameters New York Heart Association score Quality of life score Neurohormonal	Recruitment completed in 2003

In all trials, patients were having optimal medical treatment; outcomes were compared with baseline.
*P<0.05.

Even with improvements in delivery systems and pacing lead technology the site of left ventricular pacing is often limited by the individual's coronary venous anatomy. Implantation of ventricular pacemakers can be technically challenging and is associated with small risks. Inability to deploy the left ventricular lead accounts for most of the 8% reported implant failures.[16] Commonly encountered complications over and above those associated with any permanent pacemaker insertion are usually related to the insertion of the left ventricular lead. These include inability to intubate the coronary sinus or a venous tributary, dissection of the coronary sinus, displacement of the left ventricular lead, and diaphragmatic stimulation (box 3). Complications are largely minimised by the operator's experience, meticulous technique, stringent testing at implantation, and careful programming of the pacemaker at follow up.

Box 3: Limitations of the technique

- Selection of patients and prediction of patients' response
- Technical difficulties:
  Difficult anatomy
  Phrenic nerve stimulation
  Suboptimal lead placement
- Availability of expertise:
  Echo assessment
  Implanter
  Technical support
- Cost of devices

Implantable cardioverter defibrillators

Severe left ventricular dysfunction is now known to be an independent predictor of cardiac mortality. Death is usually attributable to progressive heart failure or the development of malignant ventricular arrhythmias. Several large randomised controlled trials have found a sizeable reduction in mortality among patients with ischaemic heart disease, impaired left ventricular function, and failed sudden death or evidence of ventricular arrhythmias who had an implantable cardiac defibrillator compared with patients treated with antiarrhythmic drugs.[21 22] This compelling evidence has formed the basis for guidance from the National Institute for Clinical Evidence (NICE) on widespread use of these devices in individuals at high risk.[23] The role of implantable cardiac defibrillators in patients with non-ischaemic cardiomyopathy is less certain but should be addressed by the ongoing sudden cardiac death in heart failure trial, which includes patients with both ischaemic and non-ischaemic cardiomyopathy. In the most recently published multicentre automatic defibrillator implantation II (MADIT II) trial,[24] no formal assessment of arrhythmic risk was required; the inclusion criteria were based on the presence of ischaemic heart disease and poor left ventricular function alone. The trial was stopped early because of a relative risk reduction of 31% in all cause mortality seen in the group treated with implantable cardiac defibrillators compared with controls over a 20 month follow up period. The implications of this trial alone may expand the recommended indications for implantation of these devices in the future.

Additional educational resources

- The website of the North American Society of Pacing and Electrophysiology (www.naspe.org) gives useful general information on recent developments and current guidelines for heart failure devices
- www.docguide.com is a general website citing recent literature, which has several links for cardiac resynchronisation
- The official website of the National Institute for Clinical Excellence (www.nice.org) provides full and abbreviated guidelines for the use of implantable defibrillators
- www.medtronic.com/physician/cardiology.html is an extensive website of a major device company, with sections for doctors and patients, and covers all aspects of current pacing technologies used for heart failure

In the light of trials showing a reduction in mortality with implantable cardiac defibrillators and improvement in left ventricular function with biventricular pacing in patients with heart failure it seems logical that combined biventricular pacing and implantable cardiac defibrillators devices may be complementary in selected patients. The early indications from the COMPANION trial support this theory, with the greatest reduction in mortality observed with combined devices. Although final reports are yet to be published on prospective trials incorporating combined biventricular pacing and implantable cardiac defibrillators devices, the use of combined devices to provide both cardiac resynchronisation with defibrillation are likely to increase.

Conclusion

Evidence is now compelling that pacing technologies can improve morbidity and mortality in patients with heart failure. The indication for using these devices is likely to expand in the future. Clinicians at all levels should have a fundamental knowledge of the indications and function of these devices. The growth in these technologies will also have serious economic implications for those planning and delivering health care.

Competing interests: AWCC has received reimbursement from many companies for attending conferences. REL receives a research fellowship from Medtronic Inc and has received reimbursement from many companies for attenting conferences. MRC is the clinical adviser for the national clinical guidelines on the management of heart failure, commissioned by the National Institute for Clinical Excellence, but the opinions in this review are his own and will not necessarily reflect those in the forthcoming guideline. MRC has received honorariums for advisory boards and lectures related to treatments mentioned in this review.

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Endpiece

Human dignity

Among other living things, it is man's dignity to value certain ideals above comfort, and even above life. This human trait makes of medicine a philosophy that goes beyond exact medical sciences, because it must encompass not only man as a living machine but also the collective aspirations of mankind.

René Jules Dubos (1901-81), French/American microbiologist, in *Mirage of Health*

Robert Richardson, medical historian, Chichester